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CASWELL FILE

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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NOV 16 1993

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Id# 000432-TTI. Deltamethrin: Review of a domestic animal safety study with the product "Deltamethrin 3% Collar".

pc 097805

TOX CHEM No.: 463B
PC No.: ~~097805~~ 209400
Barcode No.: D194602
Submission No.: S446520

FROM: John Doherty
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Health Effects Division (7509C)

TO: George LaRocca/John Hebert
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Registration Division (7505C)

THROUGH: Marion Copley, DVM, Section Head
Section IV, Toxicology Branch I
Health Effects Division (7509C)

Marion Copley 11/15/93

I. CONCLUSION

The domestic animal safety study with the product Deltamethrin 3% Collar was reviewed and determined to be ACCEPTABLE. No reactions to treatment were noted when one collar (4% active ingredient worn for six months), four collars (3% active ingredient worn for three months, or 4% active ingredient worn for six months) were worn.

The product has been demonstrated to be safe for adult dogs. If the registrant wishes to register the product for use on dogs less then 3 months of age an additional study using puppies of defined age will have to be presented.

II. Action Requested

The Roussel Uclaf Company (refer to letter from Sharon M. Johnson dated July 9, 1993) has submitted a domestic animal safety study (MRID No.: 428890-06) with dogs to support the registration of the product Deltamethrin 3% Collar. The study was reviewed and the following comments apply.

III. Toxicology Branch Comments

1. The study was determined to be ACCEPTABLE and to demonstrate the safety of the product to adult (see item 2 below) dogs. The study demonstrated that there were no effects of wearing 3 or 4 collars equivalent to 3 or 4 times the recommended usage rate for up to six months. Refer to the DER attached.

2. The age of the test dogs was not specified in the study report. Therefore, the product is considered to have been demonstrated to be safe for use on adult dogs (greater than 3 months of age). The product label should thus include in the precautionary statement for use on dogs of greater than 3 months of age only. Or do not use on puppies less than 3 months of age. [Note: This precautionary statment is already included on the draft label dated July 20, 1993.]

If the registrant wants to use the product on puppies less than 3 months of age, the registrant will have to provide the exact ages of the dogs used in the existing study and demonstrate that treatment was initiated at a specified age less than 3 months.

Alternatively, the registrant will have to submit a second study in which the treated puppies are of a defined age. For example, if one month old puppies are treated, and the study demonstrates the 3 fold safety factor in which no reactions are noted, the product label can be amended to include for use of puppies greater than one month of age. If this study is conducted, the puppies should not have to treated for more than two weeks and the ChE and AChE assays should not have to be included.

IV. Studies Reviewed

Study Identification	Material	MRID No.:	Results	Classification
86-1. Domestic animal safety study-dogs. Hazleton # HWA 2623-103. April 11, 1993	3% and 4% deltamethrin containing collars from lots 1103 (3%) and 1104 (4%).	428890-06	No reactions to wearing collars at 3X (for three months) and 1X and 4X (for six months). Mongrel purpose bred dogs. Control (4 collars without delta-methrin), deltamethrin treated collars: 4%, 1 collar for 6 months; 3%, 4 collars for three months and 4%, 4 collars for six months.	ACCEPTABLE. The study satisfies the requirement for a domestic animal safety study for adult dogs. An additional study may be required to support the use of this product on puppies less than three months of age.

[86-1. Dogs 4% collars/1993]

Reviewed by: John Doherty 11/15/93
Section IV, Toxicology Branch I (7509C)
Secondary reviewer: Marion Copley, DVM 11/17/93
Section IV, Toxicology Branch I (7509C)

DATA EVALUATION REPORT

STUDY TYPE: 86-1. Domestic animal safety study (6 month-dogs)

MRID NO.: 428890-06. TOX. CHEM. NO.: 463B
PC No.: 097805

TEST MATERIAL: 3% (from lot No.: 1103) and 4% (from lot 1104) deltamethrin fortified dog collars.

STUDY NUMBER(S): HWA 2623-103 and RBT No.: 91-135.

SPONSOR: Roussel Bio Corporation, Lincoln Park, New Jersey

TESTING FACILITY: Hazleton Washington, Inc.

TITLE OF REPORT: "6-Month Deltamethrin Flea and Tick Collar Safety Study in Dogs"

AUTHOR(S): Dan W. Dalgard, D.V.M.

REPORT ISSUED: April 11, 1993

STUDY DATES (in life): Initiation: November 27, 1991, Termination June 29, 1992.

CONCLUSIONS:

No reactions to wearing collars at 3X (for three months) and 1X and 4X (for six months).

Mongrel purpose bred dogs. Control (4 collars without deltamethrin), deltamethrin treated collars: 4%, 1 collar for 6 months; 3%, 4 collars for three months and 4%, 4 collars for six months.

Classification: ACCEPTABLE. The study satisfies the requirement for a domestic animal safety study for adult dogs. An additional study may be required to support the use of this product on puppies less than three months of age.

Quality Assurance Statement: Provided.
Good Laboratory Practice Statement: Provided.

[86-1. Dogs 4% collars/1993]

REVIEW

Experimental Constants:

Test Material: Deltamethrin impregnated dog collars containing 3% (from lot #1103) or 4% (from lot #1104) and placebo collars without deltamethrin (lot # 110C) obtained from the Roussel Uclaf Company.

Test System: Purpose bred mongrel dogs with both short and long hair were obtained from the Hazleton Research Products, Inc. Cumberland, Virginia. The exact age of the dogs at initiation of dosing (age of application of the collars) was not referenced in the report.

Basic Experimental Design

Four groups of 4/sex dogs which consisted of a control (placebo collar), low dose (usage rate or one collar of 4% deltamethrin, actually slightly greater than the usage rate of a 3% collar), mid dose (4 collars of 3% deltamethrin) and high dose (4 collars of 4% deltamethrin). The dogs were scheduled to wear their collars for six months. After three months, the mid dose group was terminated because there were no reactions noted in any group. The control, low and high dose groups continued for the scheduled six months.

Analytical Chemistry

1. Release rates of deltamethrin from the collars. Sections of the 3% and 4% collars were removed and analyzed for deltamethrin at pretest, at three and six months to determine the rate of release from the matrix. The Analytical report is in Appendix 11. In summary the analytical data were shown to have release rates 120 ug/collar/day for the 3% collar at the 3 month interval. The 4% collars were shown to have release rates of 40 and 251 ug/collar/day at the 3 and 6 month intervals.

2. Blood levels of deltamethrin. The blood was sampled from the dogs wearing only one collar on days 25, 51, 86 and 177 and analyzed for deltamethrin content. The limit of assay was said to be 5 ng/ml. No detectable deltamethrin was evident at days 25, 51 and 86. Although some evidence of < 5 ng/ml was noted for three dogs at day 177, the study report did not consider these readings actual (referring to them as incidental). TB-I concurs and does not consider that wearing a single collar resulted in significant levels of deltamethrin in the blood.

Assessments and Results

1. Survival and clinical signs.

The dogs were reportedly examined twice daily for mortality and once daily for behavioral reactions. In addition, a staff veterinarian examined the dogs on days 1, 8, 26, 88 and 179 (in addition to two pretreatment examinations) for dermatological and clinical evaluations including heart and respiratory rate and body temperature recordings.

All dogs survived the experiment and no treatment related findings were noted.

2. Body weight and feed consumption.

Body weight and feed consumption were reportedly assessed weekly. The study author maintains that there were no compound related effects on these parameters.

TB-I considers that the body weight and feed consumption data showed variations for which interpretation was confounded by the fact that the dogs were mongrels and of different sizes and there were only four dogs/sex/treatment group. Inspection of the growth curve for females (refer to Figure 3, photocopied from the study report attached) supports the conclusion of the study author. The male group wearing only one collar had a higher rate of growth than the other dogs. The report, however, asserts that this is related to the dogs being mixed and mongrels. Since the dogs wearing four collars (with either 3 or 4% deltamethrin) did not also show indications of similar increased weight gain, TB-I concurs that the weight gain pattern for the group wearing only one collar was not affected by the presence of the deltamethrin in the collar.

There also appeared to be an increase in feed consumption in the dogs (both sexes) wearing 4 collars with 4% deltamethrin in the later weeks of the study (refer to Figure 3 photocopied from the study report attached). TB-I does not consider that the apparent increase is conclusively related to treatment.

3. Clinical Hematology and Biochemistry

Samples of blood were taken from the jugular vein from fasted dogs on days -7, -6, -3, 2, 4, 8, 15, 22, 29, 54 and 89 and 180. for plasma ChE and RBC AChE. Blood samples for days -13, 25, 51 and 86 and 177 were also taken for hematology and serum chemistry.

A. Hematology. The following hematology parameters were reportedly investigated.

cell morphology
corrected leukocyte count
erythrocyte count
erythrocyte sedimentation rate
hematocrit
hemoglobin
leucocyte count
leucocyte differential
platelet

No consistent compound related effects were noted on any of these parameters.

B. Serum Chemistry

alanine aminotransferase (ALT
albumin
albumin/globulin ratio
alkaline phosphatase
aspartate aminotransferase
blood urea nitrogen
calcium
chloride
creatine kinase
creatinine
globulin
glucose
inorganic phosphorous
potassium
sodium
total bilirubin
total protein
RBC AChE
Plasma ChE

No consistent compound related effects were noted on any of these parameters.

There were some instances on increased RBC AChE (including in the preapplication period) and plasma ChE. Increases in the activity of these enzymes is not a recognized toxicity response. Since there was no inhibition of these enzymes and the increases were not related to the quantity of the collars worn, it is concluded that the treatment did not affect these enzymes. Moreover, ChE and AChE are not recognized as being inhibited by pyrethroids such as deltamethrin.

No necropsy was performed and is not considered necessary.

CONCLUSION (Study). The study is considered ACCEPTABLE. No additional domestic animal safety studies are required at this time. The study supports the following "one liner":

No reactions to wearing collars at 3X (for three months) and 1X and 4X (for six months).

Mongrel purpose bred dogs. Control (4 collars without deltamethrin), deltamethrin treated collars: 4%, 1 collar for 6 months; 3%, 4 collars for three months and 4%, 4 collars for six months.

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FIGURE 3 – MEAN FOOD CONSUMPTION

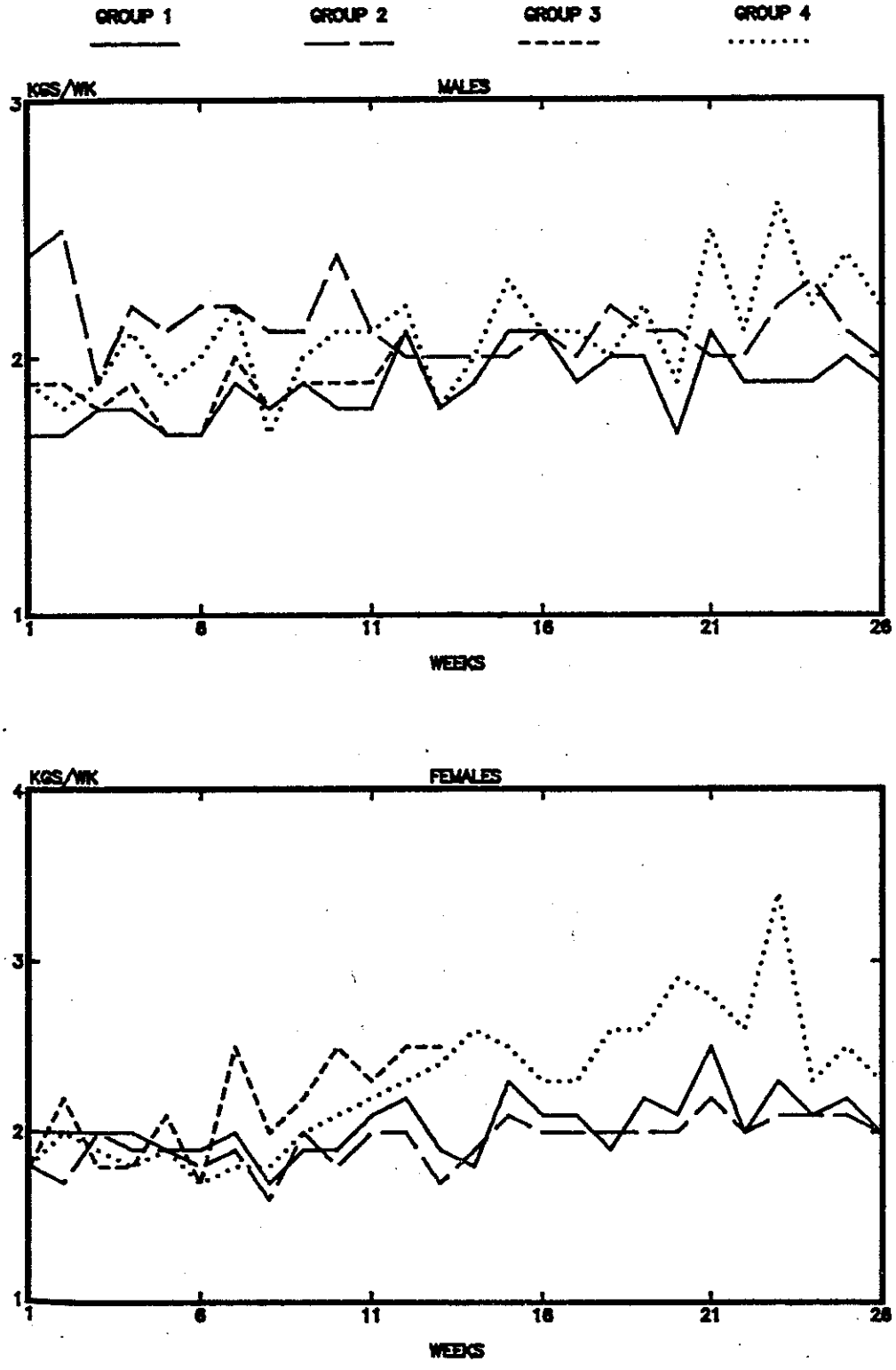

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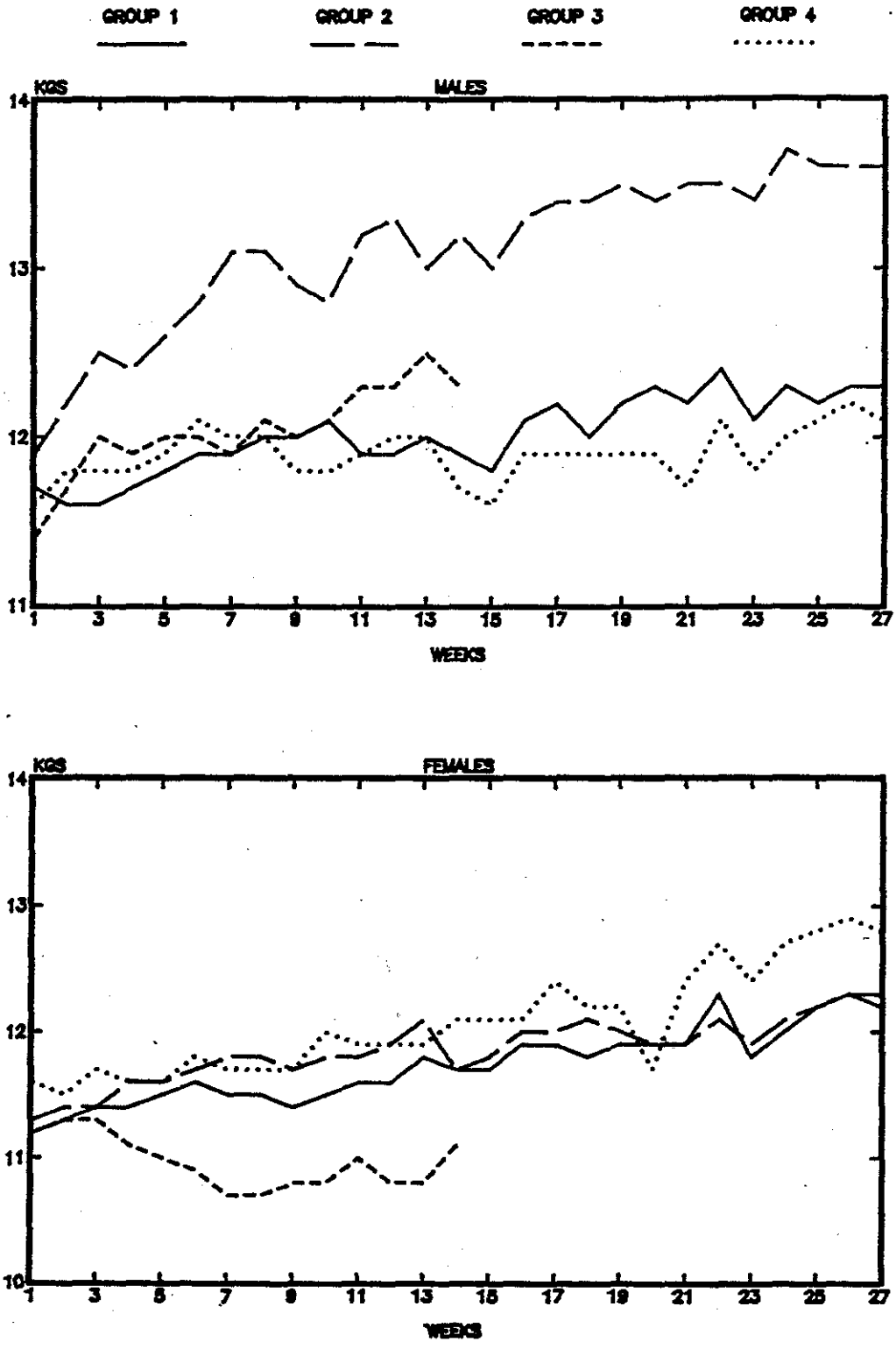
FIGURE 2 – MEAN BODY WEIGHTS



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Chemical:	**Cyclopropanecarboxylic acid, 3-(2,2-dibr**
PC Code:	**097805**
HED File Code	**13000 Tox Reviews**
Memo Date:	**11/16/93**
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04/17/2002